Lifestyle Interventions for Adults with Impaired Glucose Tolerance: A Systematic Review and Meta-Analysis of the Effects on Glycemic Control

Qing-Hai Gong, Ju-Fang Kang, Yan-Yan Ying, Hui Li, Xiao-Hong Zhang, Yan-Hui Wu and Guo-Zhang Xu

Abstract

Objective Previous meta-analyses have demonstrated that lifestyle modification can reduce the blood glucose levels in patients with type 2 diabetes, although the effects of changes in the blood glucose level on impaired glucose tolerance (IGT) remain controversial. This review therefore aimed to determine the efficacy of lifestyle interventions in adults with IGT.

Methods We searched the Medline, Cochrane Library, EMBASE and Science Citation Index databases and reference lists of the included articles. Two independent reviewers extracted the data and assessed the quality of the included studies; a total of nine randomized controlled trials met the inclusion criteria. In addition, we tested for trial heterogeneity and calculated the pooled effects size using the random effects model.

Results The overall interventions were associated with a decline in the 2-hour plasma glucose levels [standardized mean differences (SMD) -0.56; 95% confidence interval (CI), -1.01 to -0.10; F, 96.6%]. Moreover, dietary intervention (SMD -0.53; 95% CI -0.77 to -0.28) and physical intervention (SMD -0.42; 95% CI -0.63 to -0.20) were each associated with a decline in the 2-hour plasma glucose levels compared with that observed in the control participants. The overall interventions were associated with a decline in the fasting plasma glucose (FPG) levels (SMD -0.27; 95% CI -0.38 to -0.15; I² = 47.1%). In addition, physical intervention (SMD -0.25; 95% CI -0.44 to -0.05) and combined dietary and physical intervention were each associated with a decreased FPG level (SMD -0.28; 95% CI -0.44 to -0.12) compared with that observed in the control participants.

Conclusion Lifestyle modification based on physical or dietary interventions or both is associated with improvements in the 2-hour plasma glucose and FPG levels in IGT patients.

Key words: impaired glucose tolerance, intervention, meta-analysis

Introduction

Type 2 diabetes is a growing global health problem that affects millions of people every year. One study found that individuals with type 2 diabetes have a shortened life expectancy reduced by as much as 15 years, with up to 75% of patients dying of macrovascular complications (1). Approximately 347 million people were estimated to have diabetes worldwide in 2008, an increase of 194 million cases from 1980 (2). More than 80% of deaths associated with diabetes occur in low- and middle-income countries (3), and recent studies project that, by 2030, India will have 79-87 million and China will have 42-63 million adults with diabetes. The prevalence of diabetes among adults (20-79 years of age) worldwide is expected to be 7.7% or 439 million individuals in 2030. Between 2010 and 2030, it is anticipated that there will be a 69% increase in the number of adults with diabe-
Impaired glucose tolerance (IGT) is an intermediate condition in the transition from normality to diabetes. Individuals with IGT have an increased risk of disease progression to type 2 diabetes. IGT is a pre-diabetic state of hyperglycemia characteristic of peripheral insulin resistance, and it has been shown that weight loss and increases in daily energy expenditure decrease the rate of insulin resistance (6, 7). Furthermore, previous meta-analyses have demonstrated that exercise training and/or dietary modification can be used to reduce the hemoglobin A1c (HbA1c) or blood glucose levels in type 2 diabetes (8, 9). However, no meta-analyses have so far been performed to determine whether lifestyle interventions are associated with similar declines in the blood glucose levels in adults with IGT. The aim of the present systematic review and meta-analysis was therefore to examine the effects of lifestyle interventions on changes in the blood glucose levels in patients with IGT and provide a summary of these effects on the 2-hour plasma glucose and fasting plasma glucose (FPG) levels.

Materials and Methods

Search strategy and study selection

We searched the following electronic databases covering the period from January 1980 through July 2013: MEDLINE (accessed via PubMed), the Cochrane Central Register of Controlled Trials, EMBASE and the Science Citation Index. No language restrictions were applied to the search or of Controlled Trials, EMBASE and the Science Citation Index. Each of these databases was searched independently by two reviewers (G.Q.H. and K.J.F.). Disagreements were resolved via consensus or, if the difference in opinion persisted, by a third reviewer (Y.Y.Y.). We also attempted to contact the original authors of the articles to obtain missing data or clarify the data presented. Relevant data included the first author’s name, study title, year of publication, country of origin, participant age, BMI, duration of follow-up, outcome assessment, number of participants and drop outs, definition of pre-diabetes or IGT, pre and post means of intervention and mean of dispersion [standard deviation (SD), standard error of the mean (SEM) or 95% confidence interval (CI) for the intervention and control groups]. We calculated or estimated the difference in the mean and SD between the intervention and control groups for each individual study, using estimation methods based on the reference Cochrane handbook for systematic reviews (10).

Assessment of risk of bias in the included studies

We assessed internal validity based on the Cochrane methodology by examining each study for potential selection, attrition and detection bias (10). The quality assessment was independently performed by two unblinded reviewers (G.Q.H. and Y.Y.Y.), and disagreements were resolved via consensus or by a third reviewer (K.J.F.). Studies were not excluded due to poor quality.

Data analyses

Absolute changes in the blood glucose levels were reported as differences in the arithmetic mean before and after the intervention. Data obtained from intention-to-treat analyses were entered whenever available, including RCTs. All data were summarized statistically under a random effects model meta-analysis according to the method of standardized mean differences (SMD). Continuous outcomes were combined using the De-Simonian method. Heterogeneity was examined using the standard chi-squared test, with a significance level of alpha equal to 0.1, in view of the low power of such tests. Heterogeneity was also examined with the $F$, where $F$ values of 75% or more indicated a high level of heterogeneity (11). All p values were two-tailed ($\alpha=0.05$). When heterogeneity was found, we attempted to determine potential underlying causes by examining the individual study characteristics for subgroups of the main body of evidence. For all analyses, we used the Stata program (version 11.0).

Results

Description of the studies

We identified nine RCTs that met our inclusion criteria (12-20). A flow diagram of this review is depicted in Fig. 1. The literature search identified 2,311 articles; by screening the title, we excluded 198 articles. Of the remaining 2,113 articles, 2,053 were excluded based on the abstract. After reading the full text of the 60 remaining arti-

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tes in developing countries, with a 20% increase in developed countries (4, 5).

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of the nine studies are shown in Table. The size of the participant population in each study varied from 78 to 577. Six studies (13, 14, 16, 17, 19, 20) were conducted in Europe and three studies (12, 15, 18) were conducted in Asia. The mean age, diagnostic criteria, mean BMI, style of intervention and number of drop outs were compared between the studies. Overall, the mean age was 54.3 years (range, 45 to 65), the mean BMI was 28.4 (range, 24.6 to 31.2, eight studies), the mean drop-out rate was 21.1% (range, 4.0 to 44.2%) and the mean follow-up was 58 months (range, 12 to 240). Six studies (12-14, 16-18) used the criteria defined by the WHO in 1985 (21), whereas two studies (19, 20) used the criteria defined by the WHO in 2006 (22) and one study (15) used the glycogenic diagnostic criteria issued by the ADA in 2003 (23). None of the studies reported the incidence of progression to type 2 diabetes, while all studies reported the changes in the 2-hour plasma glucose and/or FPG levels from baseline to follow-up.

Risk of bias in the included studies

The risk of bias in the included trials was assessed by examining the presence of random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data, selection reporting and other forms of potential bias. All included studies were randomized controlled trials in design. Seven studies reported the method by which random sequences were generated. Six studies reported the method of allocation concealment, with only one study using blinding. Three studies reported blinding the outcome assessors, and eight studies were judged to have a low risk of bias in the assessment of incomplete outcome data. Furthermore, we judged seven studies to be at low risk of selective reporting bias and determined that other potential sources of bias carried a low risk in all included studies. An overview of the judgments of the review authors regarding each risk of bias item in the individual included studies is shown in Figs. 2 and 3.

Effects of the interventions on changes in the 2-hour plasma glucose levels

The overall associations between the interventions vs. control and reductions in the 2-hour plasma glucose levels were statistically different (SMD -0.56; 95% CI, -1.01 to -0.10; I², 96.6%; p for heterogeneity <0.001). We separately considered the effects of dietary interventions, physical interventions and combined dietary and physical interventions in reducing the 2-hour plasma glucose levels. One study demonstrated a dietary intervention to be associated with 2-hour plasma glucose reduction compared with that observed in the control group (SMD -0.56; 95% CI, -1.01 to -0.01; I², 96.6%; p for heterogeneity <0.001). We separately considered the effects of dietary interventions, physical interventions and combined dietary and physical interventions in reducing the 2-hour plasma glucose levels. One study demonstrated a dietary intervention to be associated with 2-hour plasma glucose reduction compared with that observed in the control group (SMD -0.56; 95% CI, -1.01 to -0.01; I², 96.6%; p for heterogeneity <0.001). All results are shown in Fig. 4.
Table. Characteristics of Studies of Dietary and Physical Interventions Included in this Review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mean age (years)</th>
<th>Mean of BMI (kg/m²)</th>
<th>Participants (n)</th>
<th>Average follow-up (months)</th>
<th>Country</th>
<th>Intervention</th>
<th>Care delivered to the control group</th>
<th>Drop out (%)</th>
<th>Definition of pre-diabetes and T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>45</td>
<td>25.7</td>
<td>577 subjects with IGT</td>
<td>240</td>
<td>China</td>
<td>Diet and exercise individual advice</td>
<td>Usual advice</td>
<td>30.7</td>
<td>WHO 1985 criteria</td>
</tr>
<tr>
<td>13</td>
<td>53</td>
<td>30.6</td>
<td>301 subjects with IGT</td>
<td>12</td>
<td>Sweden</td>
<td>Dietary and physical activity intervention</td>
<td>Usual advice</td>
<td>38.2</td>
<td>WHO 1985 criteria</td>
</tr>
<tr>
<td>14</td>
<td>55</td>
<td>31.2</td>
<td>522 subjects with IGT</td>
<td>38</td>
<td>Finland</td>
<td>Dietary and exercise individual advice</td>
<td>Information about diet and exercise</td>
<td>10</td>
<td>WHO 1985 criteria</td>
</tr>
<tr>
<td>15</td>
<td>51</td>
<td>24.6</td>
<td>426 subjects with IGT</td>
<td>37</td>
<td>Japan</td>
<td>Diabetes education and support</td>
<td>Information about diabetes and IGT</td>
<td>4.0</td>
<td>ADA 2003 criteria</td>
</tr>
<tr>
<td>16</td>
<td>53</td>
<td>30.6</td>
<td>301 subjects with IGT</td>
<td>60</td>
<td>Sweden</td>
<td>Dietary and physical activity intervention</td>
<td>Usual advice</td>
<td>44.2</td>
<td>WHO 1985 criteria</td>
</tr>
<tr>
<td>17</td>
<td>57</td>
<td>NR</td>
<td>78 subjects with IGT</td>
<td>24</td>
<td>UK</td>
<td>Dietary and physical activity advice</td>
<td>No dietary or physical activity advice</td>
<td>18</td>
<td>WHO 1985 criteria</td>
</tr>
<tr>
<td>18</td>
<td>45</td>
<td>25.8</td>
<td>577 subjects with IGT</td>
<td>72</td>
<td>China</td>
<td>Dietary and (or) exercise individual advice</td>
<td>Usual advice</td>
<td>8.2</td>
<td>WHO 1985 criteria</td>
</tr>
<tr>
<td>19</td>
<td>65</td>
<td>29.2</td>
<td>98 subjects with IGT</td>
<td>12</td>
<td>UK</td>
<td>Structured education program</td>
<td>Advice leaflet</td>
<td>11.2</td>
<td>WHO 2006 criteria</td>
</tr>
<tr>
<td>20</td>
<td>65</td>
<td>29.2</td>
<td>98 subjects with IGT</td>
<td>24</td>
<td>UK</td>
<td>Structured education program</td>
<td>Advice leaflet</td>
<td>25.5</td>
<td>WHO 2006 criteria</td>
</tr>
</tbody>
</table>

NR: not reported

Effects of the Interventions on the changes in the fasting plasma glucose levels

Nine studies showed physical, dietary and/or combined interventions to be associated with declines in the FPG levels (SMD -0.27; 95% CI: -0.38 to -0.15; I², 47.1%; p for heterogeneity <0.05), as compared with that observed in the control group. In the subgroup analyses, one study demonstrated the effects of dietary intervention compared with the control protocol (SMD -0.15; 95% CI: -0.39 to 0.09). In addition, three studies showed physical intervention to be associated with FPG reduction compared with that observed in the control group (SMD -0.25; 95% CI: -0.44 to -0.05; I², 0.0%; p for heterogeneity =0.64), and seven studies demonstrated that combined dietary and physical interventions were associated with FPG reduction compared with that observed in the control group (SMD -0.28; 95% CI: -0.44 to -0.12; I², 62.4%; p for heterogeneity <0.05). All results are shown in Fig. 5.

Discussion

The underlying causative mechanisms of IGT and/or type 2 diabetes are not fully understood. Apart from genetic factors, which are primarily responsible for causing diabetes, other factors appear to be responsible as well, including environmental factors and the effects of a modern lifestyle, physical inactivity, stress, etc. (24). Studies using lifestyle interventions in patients with IGT have shown that progression to type 2 diabetes can be prevented or postponed; the lifestyle interventions employed in these studies primarily emphasized physical activity and dietary modification (25). The current meta-analysis showed that structured exercise training consisting of aerobic exercise, resistance training or both is associated with HbA1c reduction in patients with type 2 diabetes. In addition, structured weekly exercise for
more than 150 minutes per week has been found to be associated with a greater decline in HbA1c and structured exercise training reduces the HbA1c level to a larger degree than advice regarding physical activity (8). Another meta-analysis showed that lifestyle intervention (dietary, physical or both) can be used to reduce the risk of type 2 diabetes in subjects with IGT and that lifestyle interventions appear to be at least as effective as pharmacological interventions (26). However, none of these meta-analyses reported an association between lifestyle interventions and changes in the blood glucose levels in patients with IGT. In contrast, our systematic review and meta-analysis suggest that lifestyle intervention is beneficial for achieving glycemic control. Furthermore, in the subgroup analysis, physical and/or dietary interventions resulted in reductions in the 2-hour plasma glucose levels in patients with impaired glucose tolerance, while physical and combined physical and dietary interventions led to reductions in the FPG levels. Our review also demonstrated that this effect differed according to the type of lifestyle intervention.

To our knowledge, this is the first systematic review to assess the association between lifestyle interventions (physi-
Figure 5. Forest plot showing the pooled SMD with 95% CI for different style interventions with respect to changes in the fasting blood glucose levels. Individual studies are represented by squares; subgroup effects are represented by diamonds. SMD: standardized mean difference, CI: confidence interval. The studies are ordered by weight. Random effects model.

Our results have important implications for both current clinical and public health practice and research. Glycemic control is an important predictor of many chronic complications of diabetes (27). According to the UK prospective diabetes study (UKPDS), each 1% reduction in HbA1c over 10 years is associated with a reduction in the risk of death related to diabetes of 21%, myocardial infarction of 14% and microvascular complications of 37% (28). These findings highlight the need for lifestyle interventions to achieve glycemic control. Because a reduction in the 2-hour plasma glucose levels in IGT patients is associated with improvements in insulin resistance and both physical and dietary interventions have favorable effects on weight reduction, waist circumference, blood lipids and blood pressure, it is expected that the combination of these interventions would result in greater metabolic effects (11, 29). Therefore, patients with type 2 diabetes or IGT should receive dietary recommendations in addition to advice regarding increasing physical activity. Taken together, these results provide important information for clinical practice (30), as confirmed by the findings of our meta-analysis.

This study is associated with several important limitations. First, this review was limited to published studies and, although subject experts were contacted in order to obtain additional unpublished literature, no such information was acquired. Second, a high level of heterogeneity was identified in the meta-analysis, particularly in the meta-analysis of the effects of the interventions on changes in the 2-hour plasma glucose levels, which were not reduced in the subgroup analyses of the combined physical and dietary intervention groups. Third, none of the studies included patients from America, Africa or India, which may limit the generalizability of our results to African or other populations. Fourth, the effects of publication bias were not assessed due to an insufficient amount of the data. Finally, no studies met all our criteria for the absence of selection, performance, attrition and detection bias in the meta-analysis, reflecting an increased risk of bias.

Further research is therefore needed to better identify effective interventions for reducing blood glucose in patients with IGT and select lifestyle interventions aimed at achieving the long-term maintenance of initial changes in behavior. This research must provide adequate information, including demographic data and detailed descriptions of the interventions (particularly the contact time in both the intervention and control groups) and health care delivery system. Furthermore, allocation must be concealed during randomization, and attention must be paid to minimizing attrition. Moreover, target populations must be described and scientifically sampled so that the results are generalizable to specific populations (28, 31). As a result, there is need for fur-
ther well-designed, double-blind RCTs from other countries and regions.

**Conclusion**

Lifestyle modification based on physical or dietary interventions or both for at least 12 months is associated with improvements in 2-hour plasma glucose and/or FPG level control in IGT patients. The number and quality of available studies is insufficient. Therefore, further well-designed, double-blind RCTs with a wide geographical range are needed.

The authors state that they have no Conflict of Interest (COI).

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